

Extended Data Figures

Extended Data Fig. 1 | c-Score^{hi} tumors are enriched in immune-related genes and genesets involved with antitumor immunity

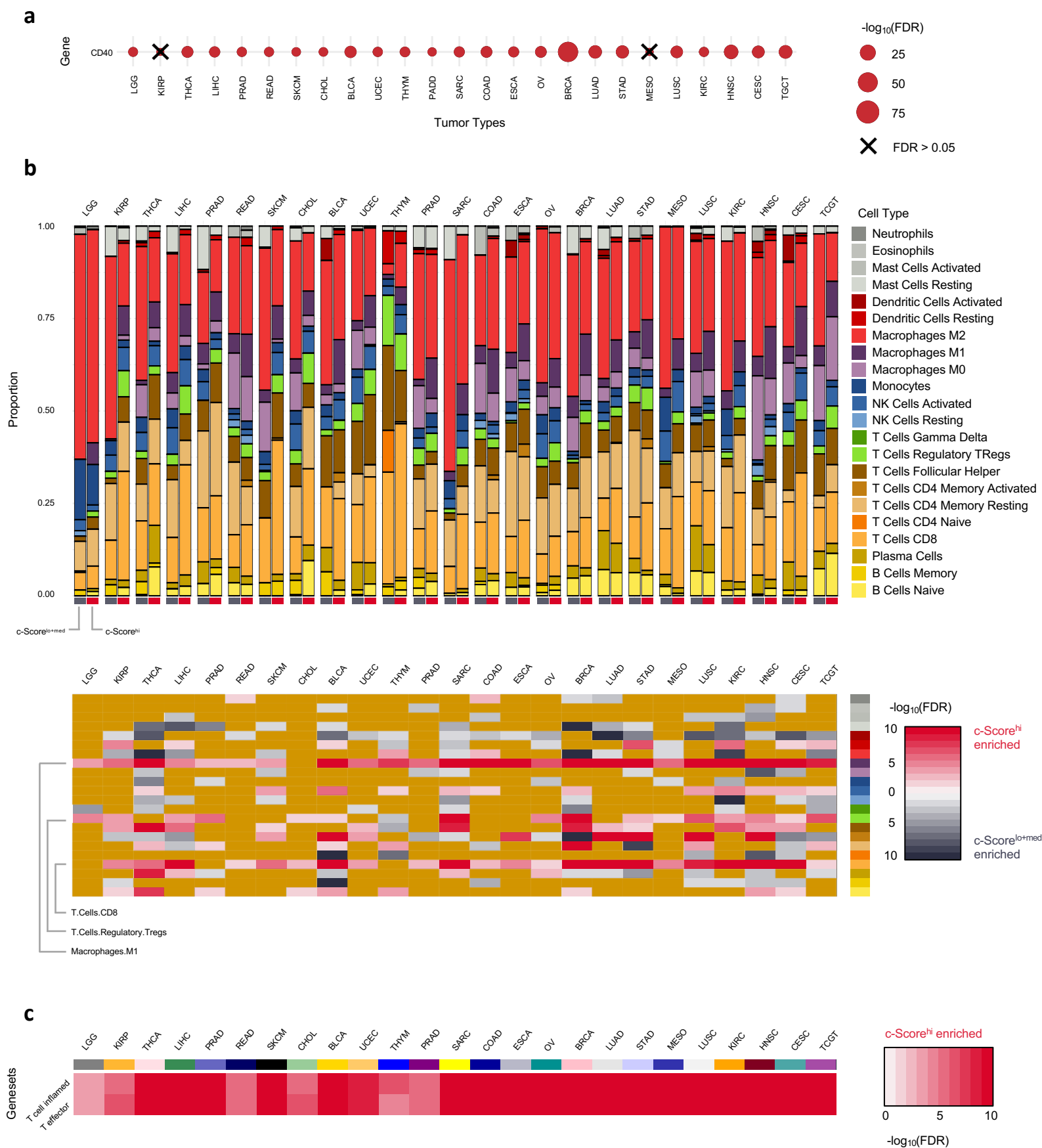
Extended Data Fig. 2 | c-Score status correlation with neoantigen load, TMB and cancer-immunity cycle gene expression

Extended Data Fig. 3 | Distribution and characteristics of c-Score in POG cohort

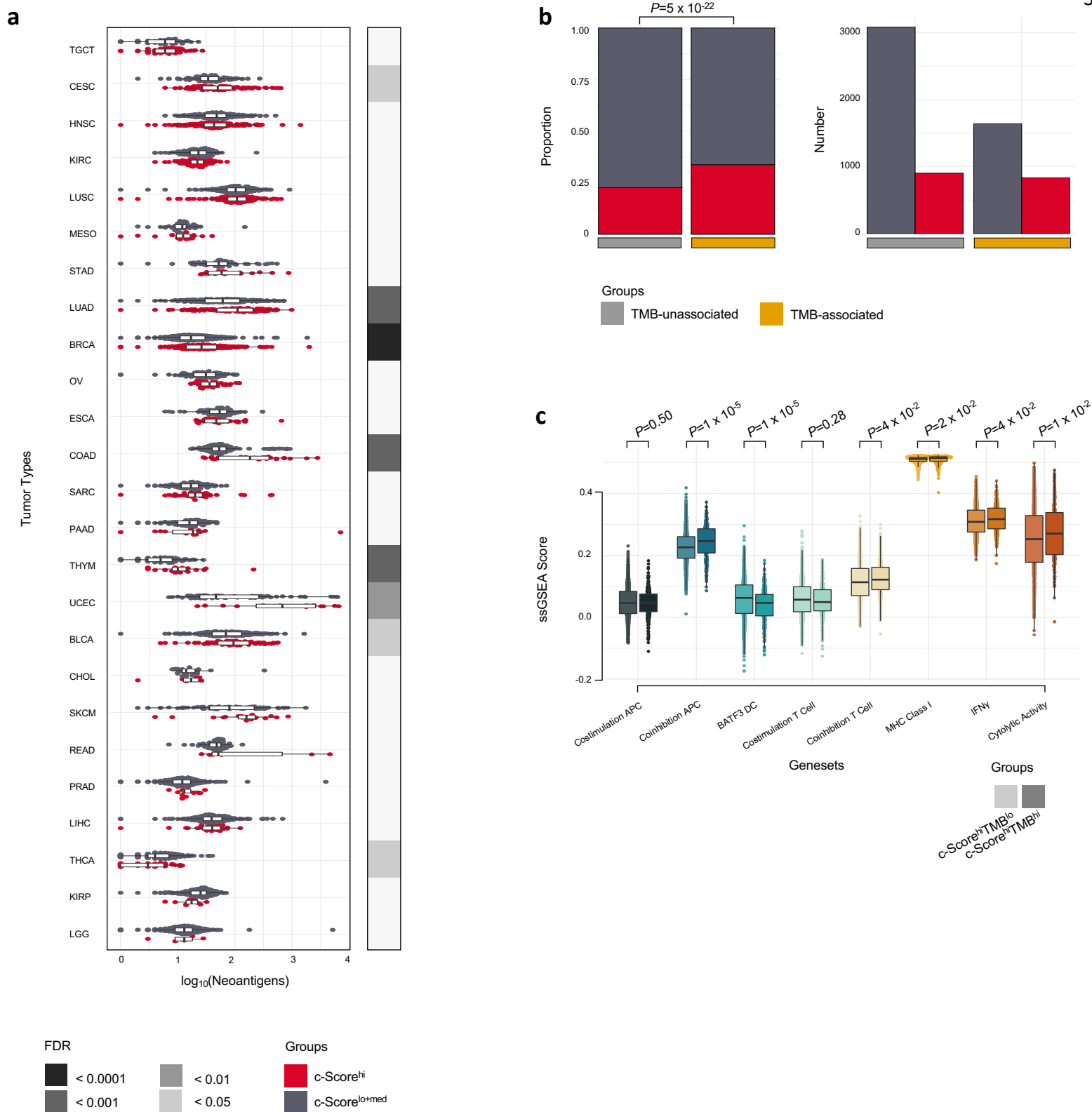
Extended Data Fig. 4 | TMB-associated subgroup has a higher proportion of tumors with mutations in DNA repair pathway mutations

Extended Data Fig. 5 | Associations between c-Score, TMB, and MSI/HRD scores

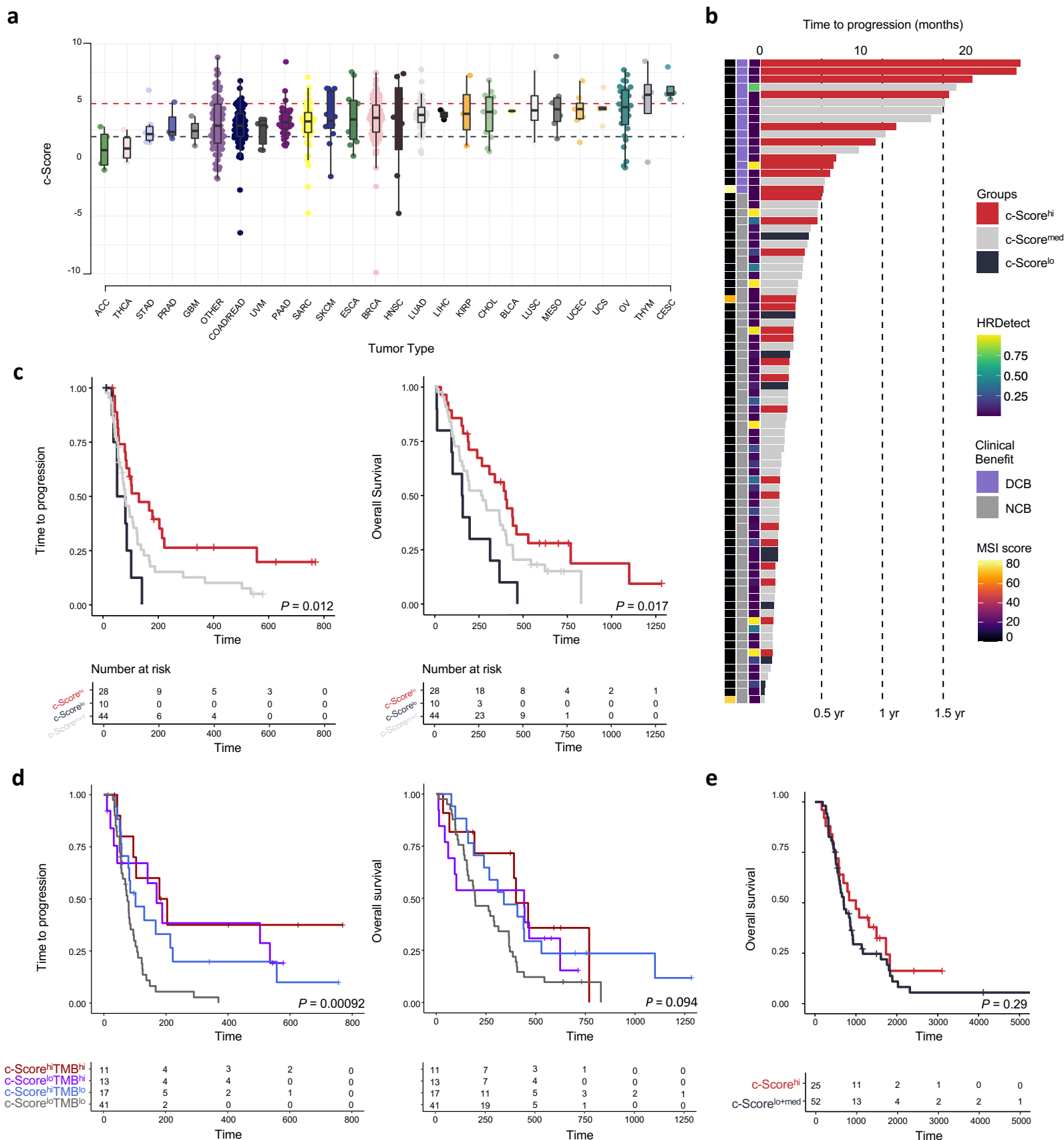
Extended Data Fig. 6 | Comparison of TMB and c-Score in wild-type versus *KRAS* mutant tumors



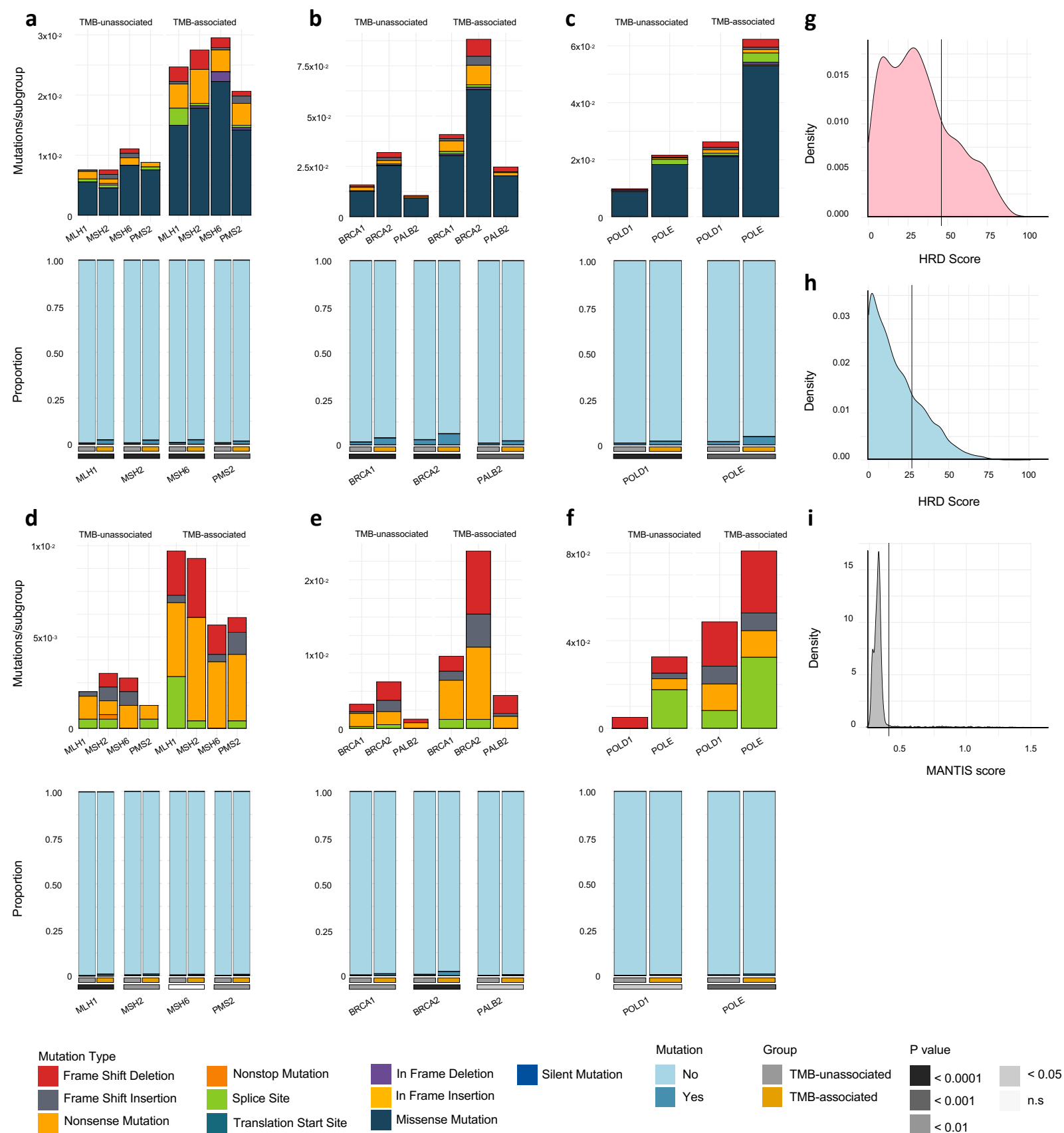
Extended Data Fig. 1 | c-Score^{hi} tumors are enriched in immune-related genes and genesets involved with antitumor immunity. **a**, Degree of significance in expression of *CD40* between c-Score^{hi} versus c-Score^{lo+med} tumors. Wilcoxon rank-sum test, FDR adjusted. X represents FDR > 0.05. **b**, Proportion of (top) and degree of significance in (bottom) CIBERSORT scores for 22 immune cell types and **c**, two genesets in c-Score^{hi} versus c-Score^{lo+med} tumors across 25 tumor types. For **b**, red and blue signify upregulation of expression in c-Score^{hi} versus c-Score^{lo+med} groups, respectively. Wilcoxon rank-sum test, FDR adjusted. Gold boxes represent FDR > 0.05.



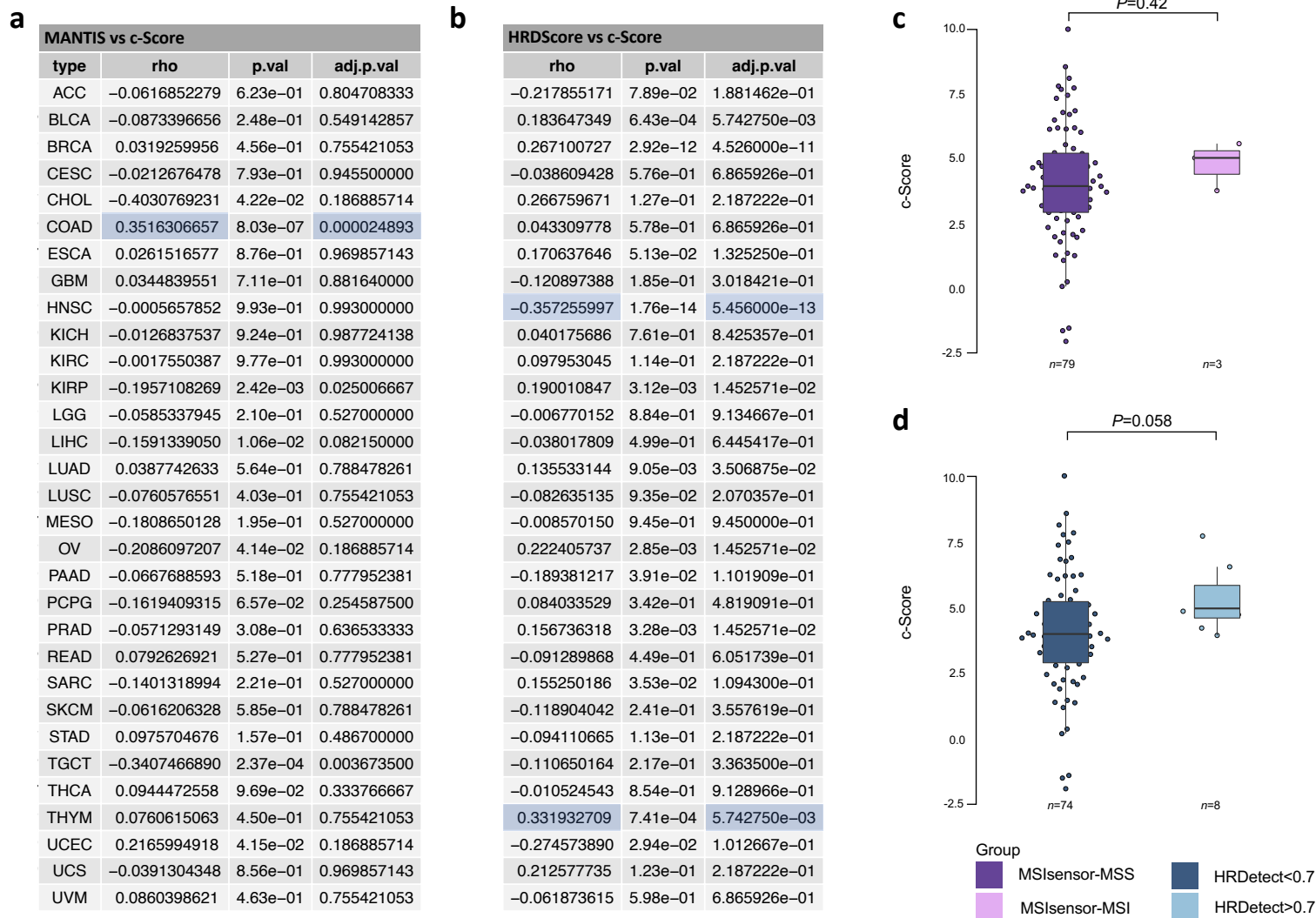
External Data Fig. 2 | c-Score status correlation with neoantigen load, TMB and cancer-immunity cycle gene expression. a, Association between SNV-derived neoantigen load and expression of the c-Score. Track displays FDR adjusted P values of SNV-derived neoantigen load differences between groups. Wilcoxon rank-sum test, FDR adjusted. **b,** The proportion (left) and absolute number (right) of $c\text{-Score}^{\text{hi}}$ and $c\text{-Score}^{\text{lo+med}}$ tumors in ‘TMB-unassociated’ versus ‘TMB-associated’. Fisher’s exact test. **c,** Comparison of ssGSEA scores across eight gene sets involved in the cancer-immunity cycle in $c\text{-Score}^{\text{hi}}\text{TMB}^{\text{hi}}$ versus $c\text{-Score}^{\text{hi}}\text{TMB}^{\text{lo}}$ tumors. Boxplot on left (light shade) and right (dark shade) of pairings are TMB^{lo} and TMB^{hi} , respectively. Wilcoxon rank-sum test, FDR adjusted.



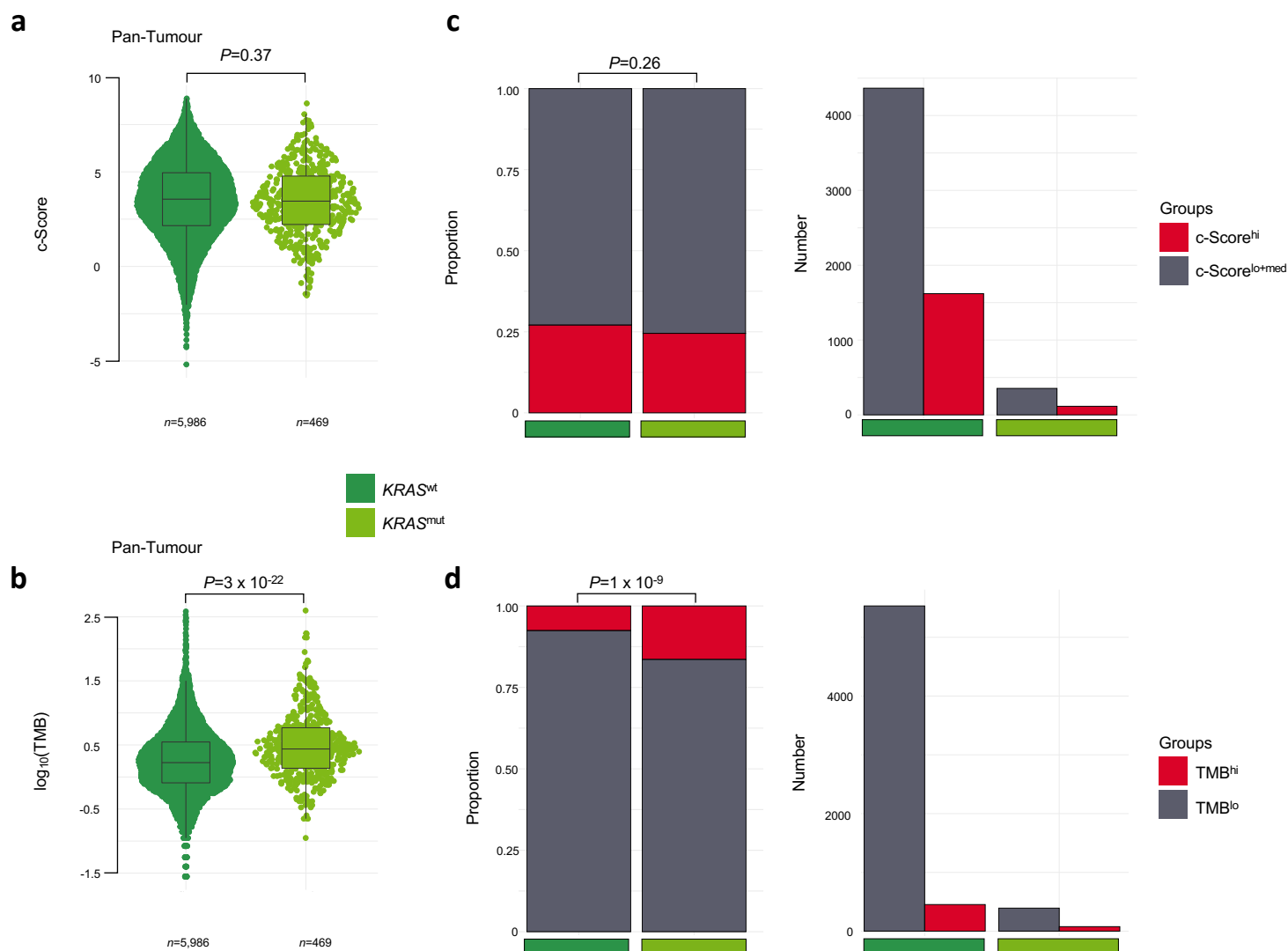
Extended Data Fig. 3 | Distribution and characteristics of c-Score in POG cohort. **a**, c-Score in POG570 cohort. Tumor types matched to TCGA nomenclature ($n=559$). OTHER refers to a mix of tumor types not specifically matching to TCGA tumor types examined in this manuscript. Dashed lines indicate where thresholds for $c\text{-Score}^{\text{hi}}$ and $c\text{-Score}^{\text{lo}}$ groups fall based on TPMs from TCGA data. **b**, Waterfall plot depicting time to progression, split by c-Score groups. HRDetect scores, durable clinical benefit (DCB), and MSIsensor scores are displayed as tracks below. Time to progression and overall survival for patients stratified by **c**, c-Score group and **d**, c-Score and TMB group. **e**, Overall survival for patients stratified by c-Score group in the POG dataset starting from date diagnosed with advanced disease ($n=77$). Log-rank test.



External Data Fig. 4 | TMB-associated subgroup has a higher proportion of tumors with mutations in DNA repair pathway mutations. **a-c**, Comparison of the total number of mutations in ‘TMB-unassociated’ *versus* ‘TMB-associated’ groups (top) and proportion of patients with any mutation (bottom) in genes analyzed, namely those involved in **a**, MMRD pathway **b**, HRD pathway, and **c**, *POLD1/POLE* genes. Graphs **d-f** depict protein-truncating mutations. Fisher’s exact test. **g,h**, Density distribution of HRD scores across **g**, BRCA and OV tumors and **h**, remaining tumor types, excluding MANTIS^{hi} tumors. Vertical lines display HRDScore^{hi} cutoffs (46 and 26, respectively). **i**, Density distribution of MANTIS scores across all tumor types, excluding HRDScore^{hi} tumors.



Extended Data Fig. 5 | Associations between c-Score, TMB, and MSI/HRD scores. a, MANTIS Score ($n=5,047$, HRDScore^{hi} tumors omitted), and **b**, HRD score ($n=6,512$, MANTIS^{hi} tumors omitted) across 31 tumor types. Spearman correlation, FDR adjusted. Comparison of c-Score in **c**, MSI sensor^{hi} versus MSI sensor^{lo} and **d**, HRDetect^{hi} versus HRDetect^{lo} tumors.



Extended Data Fig. 6 | Comparison of TMB and c-Score in wild-type versus *KRAS*-mutated tumors. **a**, c-Score and **b**, TMB wild-type versus *KRAS*-mutated tumors across the 25 tumor types. Wilcoxon rank-sum test. **c**, The proportion (left) and absolute number (right) of $c\text{-Score}^{hi}$ and $c\text{-Score}^{lo+med}$ tumors and **d**, TMB^{hi} and TMB^{lo} tumors in wild-type versus *KRAS*-mutated tumors. Fisher's exact test.